REMARKS

Upon entry of the amendments submitted herewith, claim 1 will be pending in this application. Claim 1 is under examination. Claims 2-9 have been canceled without prejudice or disclaimer to the subject matter claimed within.

Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

To better define the claimed subject matter, claim 1 has been amended to recite "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide taken from a sample of said suspension after it is autoclaved is 95% or more compared to that before it is autoclaved irrespective of whether the sample is taken from the upper, middle or lower portion of the suspension in bulk."

This amendment has basis in the specification on page 11, 2nd paragraph, on page 13, 1st paragraph, in "Table 3" on page 14, as well as in "Figure 2".

No new matter has been added within the meaning of 35 USC § 132.

In view of the aforementioned amendment and the following remarks, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claim 1 has been rejected under 35 USC § 103(a) as being unpatentable over Karlsson et al. (US Patent Publication No. 2002/0065256) in view of the MSDS for Metolose 60SH.

The Examiner maintains that the combined teachings of the Karlsson et al. reference and the MSDS for Metolose 60SH render pending claim 1 obvious under 35 USC §103(a). In view of the remarks set forth herein, this rejection is respectfully traversed.

a. <u>No prima face case of obviousness</u>

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the

prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Also, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Further, the Examiner must adhere to the requirements set forth by the U.S. Supreme Court in *Graham v. John Deere* wherein the court determined that four factors should be applied when establishing whether obviousness exists:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims at issue;
3. Resolving the level of ordinary skill in the pertinent art; and
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

i. Presently claimed subject matter

Presently pending claim 1 is directed to "An autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide taken from a sample of said suspension after it is autoclaved is 95% or more compared to that before it is autoclaved irrespective of whether the sample is taken from the upper, middle or lower portion of the suspension in bulk."

ii. Teachings of the cited art

Karlsson et al. teach that the presently claimed subject matter is "unsatisfactory" and "unacceptable". In particular, at [0009], Karlsson et al. state the following:

> "We have also found that attempts at **terminal sterilization of the pharmaceutical formulations, especially suspensions, e.g. aqueous**

> **suspensions, of glucocorticosteroids** have all proved **unsatisfactory**. Such suspensions can not normally be sterilized by sterile filtration as most of the particles of glucocorticosteroid will be retained on the filter. We have also shown that **moist heat sterilization, e.g. steam treatment of glass vials containing the product**, leads to an **unacceptable** change in particle size." (emphasis added)

As a result of Karlsson et al.'s understanding of the problems associated with autoclaving of suspensions comprising glucocorticosteroids, i.e. "terminal sterilization of the pharmaceutical formulations", Karlsson et al. teach that the "effective sterilization of dry glucocorticosteroids can be carried out at a significantly lower temperature than that considered necessary for the heat sterilization of other substances." *See* Karlsson et al. [0012]

Further, Karlsson et al. only teach that glucocorticosteroids can be heat treated as a dry powder. Only after the glucocorticosteroid is sterilized is it added to a pharmaceutical formulation such as a suspension. In this regard, Karlsson et al. teach at [0013]:

> "[T]here is provided a process for the sterilization of a glucocorticosteroid, which process comprises heat treating the glucocorticosteroid in the form of a powder at a temperature of from 100 to 130° C… preferably for up to about 24 hours, more preferably up to 10 hours, e.g. from 1 to 10 hours." (emphasis added)

Further, Karlsson et al. teach at [0044]:

> "A sterile pharmaceutical formulation comprising a glucocorticosteroid…sterilized according to the present process, can be prepared by mixing the sterilized glucocorticosteroid with any suitable ingredient, e.g. a surfactant, a pH regulating or chelating agent, an agent rendering the suspension isotonic or a thickening agent. All components, other than the glucocorticosteroid, can be produced by sterile filtration of their aqueous solutions." (emphasis added)

Applicants also note the Examples contained in the Karlsson et al. reference. Example 1 in paragraph [0048] states:

> "Nine 50g batches of micronized budesonide…were subjected to the heat treatment shown in Table 1 in a dry sterilizer…".

Example 2 in paragraph [0051] states that the samples used therein were

> "subjected to a temperature of 110°C for 3 hours and 10 min … using the same technique as in Example 1."

In Example 4, Karlsson et al. introduced the already sterilized, dry glucocorticosteroid into a formulation. In paragraph [0056], Karlsson et al. state that

> "A formulation comprising finely divided budesonide sterilized by the method of Example 2…was prepared by mixing the following ingredients…"

Particularly relevant is the disclosure of Karlsson et al. in paragraph [0057] which states:

> "All the components, other than the budesonide, were produced by sterile filtration of their aqueous solutions and an appropriate volume of the resulting suspension (about 2ml) was filled under aseptic conditions into presterilized 5ml containers to produce a sterile product." (emphasis added)

iii. Differences between the presently pending claims and the Karlsson et al. reference

First, applicants respectfully note that the newly introduced claim limitation "irrespective of whether the sample [of ciclesonide] is taken from the upper, middle or lower portion of the suspension in bulk" is not taught or suggested anywhere in the Karlsson et al. reference.

Further, applicants respectfully note that the presently pending claims recite "An autoclaved sterile aqueous suspension…". Upon reading of the presently pending claim, it is clear that the aqueous suspension is autoclaved to render the suspension sterile.

As applicants have repeatedly stated in prior Responses and Amendments, Karlsson

et al. do not teach such an autoclaved sterile aqueous suspension product. In fact, Karlsson et al. do not teach autoclaved products at all. Even more, Karlsson et al. teach the ordinary skilled artisan away from an autoclaved aqueous suspension as presently claimed.

At page 3, the Examiner refers to the requirements under *Graham v. John Deere* – namely that he must consider "the scope and contents of the prior art" and "[ascertain] the differences between the prior art and the claims at issue" in determining whether a *prima facie* case of obviousness exists. While the Examiner is correct that he must consider these requirements, the Examiner has respectfully misapplied the teachings of the Karlsson et al. reference in making his allegation that a *prima facie* case of obviousness has been established by ignoring the teachings contained in Karlsson et al. In particular, the Examiner has misconstrued portions of the Karlsson et al. reference that would clearly teach the ordinary skilled artisan away from arriving at the presently claimed subject matter.

As pointed out in the previous Response filed May 13, 2010, a careful reading of the Karlsson et al. reference makes it clear that the products taught by Karlsson et al. are very different than the product that is presently claimed. Particularly noteworthy is the teaching contained in Karlsson et al. that attempts to arrive at the presently claimed subject matter were "unsatisfactory" and "lead to an unacceptable change in particle size". (See [0009])

In this regard, applicants respectfully note the Examiner's statement at page 6 of the Official Action that:

> "Applicants have failed to show how this teaching (e.g. "an unacceptable change in particle size" [0009]) necessarily diverges from the instantly claimed invention or in any way relates to the amount of ciclesonide in the composition."

In order to clarify for the Examiner how this teaching contained in the Karlsson et al. reference actually would teach the ordinary skilled artisan away from practicing the presently claimed subject matter, applicants have submitted herewith, in an Information Disclosure Statement, a copy of the reference entitled "*Effect of drug particle size on content uniformity of low-dose solid dosage forms*" by Zhang et al. published in the International Journal of Pharmaceutics, vol. 154, pp. 179-183 (1997).

The Zhang et al. IDS reference states on page 179, in the paragraph that bridges columns 1 and 2:

> "For low-dose solid dosage forms, individual drug particles that are generated from conventional milling methods can be large enough to represent a significant portion of the dose. These large particles can be present in a blend in numbers too low to be found in every unit dose. When one or more of these particles are found in a single unit dose, the observed potency can fall outside of the desired potency limits. This problem cannot be solved by mixing and the larger drug particles must be reduced in size before attempting to make a homogeneous blend."

Thus, Zhang et al. recognize that if particles of a drug are at an undesirable size, a homogeneous blend of the dosage form may not be possible and that the "observed potency can fall outside the desired potency limits."

As such, a person of ordinary skill in the art – after reading the disclosure contained in [0009] of the Karlsson et al. reference – would be taught away from preparing the presently claimed subject matter. In particular, the person of ordinary skill in the art would recognize that "an unacceptable change in particle size" as taught by Karlsson et al. would prevent the successful preparation of a homogeneous blend of ciclesonide as presently claimed.

Again, it is well established that portions of a reference arguing against or teaching

away from the claimed subject matter must be considered. See *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416 (Fed. Cir. 1986). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the application". *In re Gurley*, 31 USPQ2d 1130 (Fed. Cir. 1994). A reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. See *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

Thus, the rule of law clearly requires that the Examiner consider a reference in its entirety in determining the scope and content of the reference. See *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, (Fed. Cir 1983), *cert. denied*, 469 U.S. 851 (1984). The Examiner therefore must acknowledge any disclosure in the reference that teaches away from the presently pending claims. *Id.* It is absolutely clear that the Karlsson et al. reference teaches a completely different product than the product presently claimed and the Examiner has not acknowledged this as required by *W.L. Gore & Assocs., Inc. v. Garlock, Inc*.

In view of the teaching contained in Karlsson et al. that "an unacceptable change in particle size" is the result of the autoclaving of suspensions of glucocorticosteroids, a person of ordinary skill would certainly be taught away from trying to prepare the presently claimed subject matter. In other words, a person of ordinary skill "would be led in a direction divergent from the path that was taken" by applicants per *In re Gurley* if she was attempting to prepare "an autoclaved sterile aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose, wherein the concentration of the ciclesonide taken from

a sample of said suspension after it is autoclaved is 95% or more compared to that before it is autoclaved irrespective of whether the sample is taken from the upper, middle or lower portion of the suspension in bulk."

Therefore, if the Karlsson et al. reference teaches anything, it teaches that a person of ordinary skill in the art cannot make the presently claimed subject matter.

To summarize, Karlsson et al. does not teach each and every element of the presently claimed subject matter as required by *In re Wilson*. Instead, Karlsson et al. teach away from the presently claimed subject matter. Further, Karlsson et al. provides absolutely no teaching that would motivate the skilled artisan to prepare the presently claimed product as required by *KSR*. Without such teaching, there can be no such expectation of success as required by *Amgen v. Chugai*. Indeed, Karlsson et al. teaches that attempts to arrive at the presently claimed subject matter were unsuccessful.

These deficiencies are not remedied by the secondary reference – the Material Safety Data Sheet (MSDS) for Metalose 60SH.

Specifically, the MSDS discloses various properties of hydroxypropylmethylcellulose Metalose 60SH. It does not contain any disclosure regarding an autoclaved sterile aqueous suspension comprising ciclesonide as presently claimed.

Therefore, no *prima facie* case of obviousness has been established over the presently pending claims.

b. Unexpected results

Despite the clear lack of a *prima facie* case of obviousness based on the teachings of Karlsson et al. and the MSDS for Metolose 60SH, if the Examiner maintains that a *prima facie* case of obviousness has been established against the presently claimed subject

matter, applicants respectfully submit that the data contained within the specification successfully rebuts this finding.

It is again respectfully submitted that the unexpected results presented in the specification clearly rebuts any *prima facie* case of obviousness alleged by the Examiner. The data illustrates that the improvement achieved by the presently claimed subject matter is more than the routine optimization of parameters that a person of ordinary skill in the art would have employed.

It is known in the art that drug content uniformity, *i.e.* uniform drug concentrations sampled from the upper, middle and lower portion of the suspension, of an aqueous suspension containing a water-insoluble drug tends to be decreased by autoclaving, even if the drug is chemically stable. *See,* for example, page 3 of the present specification. Applicants submit that the presently claimed ciclesonide-containing aqueous suspension comprising hydroxypropylmethylcellulose achieved unexpectedly superior ciclesonide concentration uniformities as compared to suspensions comprising other wetting agents.

In this regard, applicants again respectfully draw the Examiner's attention to the data in Table 3 on page 14 of the present specification. The data in Table 3 shows ciclesonide concentration uniformity after autoclaving for a ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as recited in currently amended claim 1 and exemplified by Example 2, compared to ciclesonide aqueous suspensions containing other wetting agents. The recovery rate of ciclesonide after autoclaving was calculated by taking the ciclesonide concentration before the autoclaving to be 100%. Aliquots of the bulk suspension were sampled from the upper, middle and lower portions of a glass container.

As can be seen from the calculated ciclesonide recovery rates for Example 2 and

Comparative Examples 3-7, the ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as presently claimed, achieved unexpectedly superior ciclesonide concentration uniformity as compared to ciclesonide aqueous suspensions containing other wetting agents. In particular, the standard deviation of the ciclesonide recovery rates for the upper, middle and lower portions of the bulk suspension of Example 2 is approximately 0.05%, compared to standard deviations of as high as 7% for the upper, middle and lower portions of the bulk suspension of the Comparative Examples.

Accordingly, Applicants respectfully submit that the ciclesonide aqueous suspension containing hydroxypropylmethylcellulose, as presently claimed, achieved unexpectedly superior ciclesonide concentration uniformity as compared to ciclesonide aqueous suspensions containing other wetting agents.

As a result, it is again respectfully submitted that the unexpected results presented in the specification clearly rebuts any *prima facie* case of obviousness alleged by the Examiner. Reconsideration and withdrawal of this rejection is respectfully requested.

II. At page 4 of the Official Action, claim 1 has been rejected under 35 USC § 103(a) as being obvious over Karlsson et al. (US Patent Publication No. 2002/0065256) in view of Nagano et al. (WO 01/28563).

The Examiner asserts that the combined teachings of the Karlsson et al. reference and the Nagano et al. reference describe each and every element of presently pending claim 1, thereby rendering claim 1 obvious. In view of the remarks set forth herein, this rejection is respectfully traversed.

A brief outline of relevant authority is set forth above in Section I. Also, the Karlsson

et al. reference is discussed in detail in Section I. For the sake of brevity, the discussion of the relevant authority and the Karlsson et al. reference is incorporated herein in its entirety.

The Examiner relies on Nagano et al. for its disclosure of a combination of ciclesonide and HPMC. However, Nagano et al. do not remedy the deficient teachings of Karlsson et al., discussed in Section I above.

Claim 1 is free of the prior art for the reasons discussed above (*See*, Section I) and applicant's arguments stated above are incorporated herein by reference in their entirety. Nagano et al. do not remedy the deficient teachings of Karlsson et al. because they do not teach an autoclaved sterile aqueous suspension comprising ciclesonide as presently claimed. In fact, Nagano et al. are completely silent regarding sterilized products. Therefore, they cannot possibly remedy the deficient teachings of Karlsson et al.

Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been established. If the Examiner insists that he has established a *prima facie* case of obviousness, the data contained in the present specification and discussed above in Section I of this Response and Amendment, successfully rebuts any such finding.

Reconsideration and withdrawal of this rejection is respectfully requested.

III. At page 7 of the Official Action, claim 1 has been newly rejected under 35 USC § 103(a) as being unpatentable over Nagano et al. (WO01/28563) and Suzuki et al. (JP 2001-048807) and in further view of the Wikipedia entry for difluprednate.

The Examiner asserts that the combined teachings of the Nagano et al. reference and the Suzuki et al. reference describe each and every element of presently pending claim 1, thereby rendering claim 1 obvious. In view of the remarks set forth herein, this rejection is respectfully traversed.

A brief outline of relevant authority is set forth above in Section I. Also, the Nagano et al. reference is discussed in Section II. For the sake of brevity, the discussion of the relevant authority and the Nagano et al. reference is incorporated herein in its entirety.

Applicants respectfully traverse this rejection. The Examiner asserts that the presently claimed composition would be obvious because Nagano et al. teaches the combination of ciclesonide and HPMC and because Suzuki et al. teaches autoclaving.

a. The Suzuki et al. reference contains an insufficient teaching to enable a person of ordinary skill to arrive at the presently pending claims

However, the Examiner's assertion that Suzuki et al. reference "teaches" autoclaving, based on a mere one sentence disclosure in paragraph [0015] regarding different possible sterilization techniques – including filter sterilization, autoclaving and fractional sterilization – is tenuous at best. The Suzuki et al. reference contains no real teaching that would enable a person of ordinary skill in the art to arrive at the presently claimed autoclaved suspension. It is mere speculation on the Examiner's part to assert that autoclaving any of the different medicines disclosed by Suzuki et al., let alone corticosteroids in particular, would be successful. There are no working examples that teach the skilled artisan how to sterilize any of the medicines listed in Suzuki et al. - much less autoclaving of a corticosteroid - by autoclaving and obtaining a stable sterilized suspension.

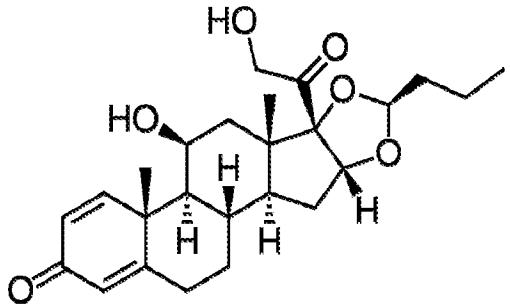
Accordingly, the Suzuki et al. reference contains a wholly insufficient teaching as to how to arrive at the presently claimed composition.

b. Chemically similar structures do not dictate similar results

Further, even if the Suzuki et al. reference contained a sufficient teaching regarding how to autoclave a corticosteroid and obtain a suitable suspension, it would not necessarily mean that the presently claimed autoclaved sterile suspension comprising ciclesonide would be an obvious result of that teaching.

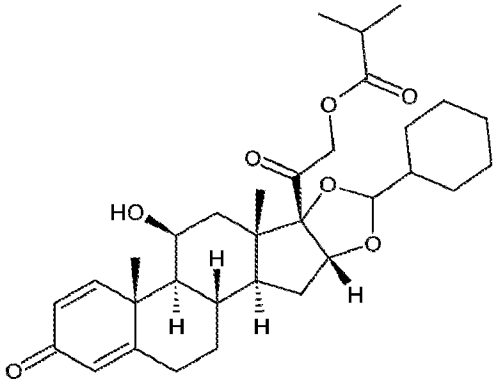
The Examiner alleges that, because ciclesonide and difluprednate "share very similar core ring structures, including bonding two acetyl groups bound at the same point on the 5-membered ring of the structure". Actually, difluprednate is not as chemically similar to ciclesonide as is budesonide which is also disclosed by Suzuki et al. on page 3 of the machine translation.

Budesonide has the following chemical formula:



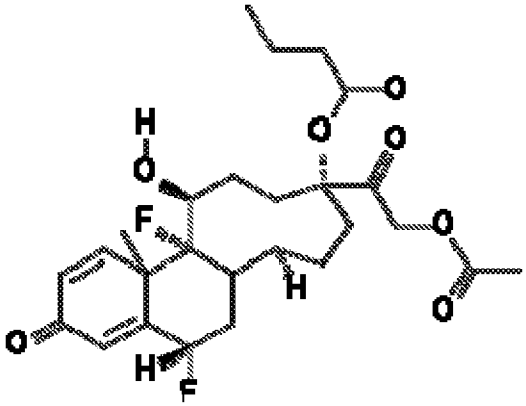
BUDESONIDE

Ciclesonide has the following formula:



CICLESONIDE

Difluprednate has the following formula:



DIFLUPREDNATE

Specifically, budesonide is more chemically similar to ciclesonide than is difluprednate because both budesonide and ciclesonide share an additional 16,17-acetal five-membered ring bonded directly to the five-membered ring of the core ring structure.

It is known that the presence of an acetal structure at the 16 and 17 positions may lead to chemical instability at high temperatures. See page 3, lines 8-10 of the specification which states that:

> "[C]iclesonide did not seem to be stable chemically at such high temperature, because ciclesonide has an acetal structure in its 16 and 17 positions."

Therefore, to follow the Examiner's reasoning that chemically similar compounds (such as difluprednate and ciclesonide) will behave similarly under similar conditions, a person of ordinary skill in the art would expect that a compound which has an acetal structure at the 16 and 17 positions would not be chemically stable.

Applicants respectfully direct the Examiner's attention to pages 9-10 of the present specification in Example1, Investigation 1 and Table 1. Example 1, a white, uniform aqueous suspension comprising ciclesonide and HPMC according to the presently pending claims was prepared. Comparative Examples 1 and 2 were also prepared. Comparative Example 1 was identical to Example 1, except that budesonide was used instead of ciclesonide. Similarly, Comparative Example 2 was identical to Example 1, except that beclomethasone dipropionate was used instead of ciclesonide. Each of the Comparative Examples were white and uniform.

Investigation 1 determined the chemical stability of the corticosteroid drugs in the aqueous suspension after being autoclaved. The results of Investigation 1 are outlined in Table 1. Table 1 indicates that ciclesonide was recovered at a rate of 100.1%. However, the chemically similar budesonide was recovered at a rate of only 26.3%. Beclomethasone dipropionate was recovered at a rate of only 78.1%. The recovery rates for Example 1 and Comparative Examples 1 and 2 were all calculated according to the same method.

This data clearly rebuts the Examiner's position that chemically similar compounds (such as budesonide and ciclesonide) will behave similarly under similar conditions. While ciclesonide proved to be chemically stable during autoclaving, the chemically similar compound budesonide was not. In particular, as a result of budesonide's chemical

instability, the budesonide level diminished by almost 75%.

Therefore, even if the Suzuki et al. reference contained a sufficient teaching regarding how to autoclave a corticosteroid and obtain a suitable suspension, it would not necessarily mean that the presently claimed autoclaved sterile suspension comprising ciclesonide would be an obvious result of that teaching. A person of ordinary skill in the art would not expect ciclesonide to possess such unexpected superior chemical stability over chemically similar compounds such as budesonide.

Accordingly, the presently claimed suspension product is not *prima facie* obvious over the disclosures contained in Nagano et al. and Suzuki et al. If the Examiner maintains that the presently claimed subject matter is obvious over these references, it is again respectfully submitted that the unexpected results presented in the specification clearly rebuts any *prima facie* case of obviousness alleged by the Examiner. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the foregoing, Applicant submits that the application is now in condition for allowance. If the Examiner believes the application is not in condition for allowance, Applicant respectfully requests that the Examiner contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

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